

CLAIMS:

1. A method of identifying modulators of AMPK-mediated activation of a nitric oxide synthase enzyme selected from the group consisting of eNOS, nNOS and nNOS μ , comprising the step of testing putative modulators for their ability to increase or decrease phosphorylation of the enzyme, said increase or decrease depending on the calmodulin and calcium ion concentrations.

2. A method according to claim 1, in which the specific phosphorylation of Ser-1177 is assessed in the presence of calcium and calmodulin.

3. A method of identifying modulators of AMPK-mediated inhibition of eNOS, comprising the step of testing a putative modulator for its ability to decrease or increase AMPK-mediated phosphorylation of eNOS in the presence of limiting calcium ions.

4. A method according to claim 3, in which the specific phosphorylation of Thr-495 is assessed.

5. A method according to any one of Claims 1 to 4, in which one or more of the following activities is additionally assessed:

- (a) Effect on smooth muscle contraction;
- (b) Effect on inotropic activity of the heart;
- (c) Effect on chronotropic activity of the heart; or
- (d) Effect on platelet function.

6. A method according to any one of Claims 1 to 5, in which the modulator is an activator, as herein defined.

7. A method according to Claim 6, in which the activator promotes both glucose metabolism and fatty acid metabolism.

- 29 -

8. A method according to any one of Claims 1 to 5, in which the modulator is an inhibitor, as herein defined.

9. A method according to any one of Claims 3 to 8, in which the modulator acts preferentially on non-neuronal cells.

10. A method according to Claim 1 or Claim 2, in which the modulator promotes the dephosphorylation of Ser-1177 and inhibits eNOS activity.

11. A method according to Claim 3, in which the modulator promotes the dephosphorylation of Thr-495 and stimulates eNOS activity.

12. A method according to Claim 1 or Claim 2 in which the modulator promotes phosphorylation of nNOS or nNOS μ at Ser-1417.

15 13. A method according to Claim 1 or Claim 2 in which the modulator promotes dephosphorylation of nNOS or nNOS μ at Ser-1417.